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The effectiveness of zoledronic acid and ibandronic acid as therapy for bone metastases in multiple myeloma: A systematic review

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ABSTRACT

Zoledronic acid and ibandronic acid are used in preventing skeletal-related event (SRE) in multiple myeloma (MM). Both drugs were listed in the Indonesian formulary. There was no available head-to-head comparative study, hence the need for a systematic review. The purpose of this systematic review was to describe the effectiveness of intravenous zoledronic and ibandronic acids in preventing SRE. The search for articles was conducted on accessible databases with the potential to provide relevant research material such as PUBMED, EBSCOhost, and ScienceDirect. The articles were limited to randomized controlled trials on both drugs in MM patients, published between 1980 and 2018. The outcomes were SRE, progression-free survival (PFS), overall survival (OS), and adverse event (AE). Thirteen articles were selected. According to the results obtained, the effectiveness of zoledronic acid in preventing SRE was superior to placebo or clodronic acid but not superior to denosumab and pamidronic acid. Ibandronic acid was not superior to placebo or pamidronic acid. The effectiveness of both drugs in preventing SRE was directly proportional to PFS and OS. In conclusion, zoledronic acid was superior to ibandronic acid, but with more occurrence of AE. However, the AE could be reduced by prolonging the duration of the drug use.

INTRODUCTION

Bone metastases are common occurrence in people with multiple myeloma (MM), which could cause skeletal-related events (SRE) such as fractures, spinal cord compression, need for radiotherapy and bone surgery (Union for International Cancer Control, 2016). According to Geng *et al*. (2015), there is a need for therapy considering the fact that these conditions affect the quality of life of the patients.

The bisphosphonate compounds have been found to be effective in the treatment symptomatic of bone disease. These compounds do not only prevent bone loss but also reduce musculoskeletal symptoms (Saroja and Ram, 2017). Also, in clinical practice, they are used for MM patients at stage I with annual skeletal surveys, bone densitometry, and other metabolic tests (NCCN, 2018). Zoledronic acid and ibandronic acid given intravenously are the bisphosphonate compounds included in the Indonesian National Formulary.

Zoledronic acid is a third-generation amino-bisphosphonate, which is stronger than the non-nitrogen bisphosphonates such as etidronate and clodronate (Alegre *et al*., 2013). Also, Gabbert *et al*. (2014) and Weide *et al*. (2010) reported that the Zoledronic acid is recommended in several therapeutic guidelines for MM in preventing SRE; however, it often comes with the osteonecrosis of the jaw (ONJ) and the incidence of kidney disorders as an adverse event (AE). Then, the ibandronic acid is used in treating hypercalcemia in solid tumors (Alegre *et al*., 2013). The European Union in 2003, approved the use of zoledronic acid in treating metastatic breast cancer, inhibit osteoclast activity and resorption of bone which causes apoptosis. The adverse effects of using ibandronic acid include diarrhea, nausea, and kidney toxicity. According to Geng *et al*. (2015), the most signifiant risks are abdominal pain and ONJ.

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However, in the occurrence of ONJ, the use of both drugs must be stopped, which could be continued once the patient recovers. Also, there is a need for the determination of creatinine serum levels, assessment of clinical symptoms, and conducting monthly blood tests as long as the drugs are in use. Other adverse drug reactions, reported according to Alegre *et al*. (2013), include nausea, vomiting, flu-like symptoms, arthromyalgia, bone pain, and hypocalcemia.

Also, there is a need for the assessment of the effectiveness of these drugs on SRE prevention, overall survival (OS), progression-free survival (PFS), and safety. This is usually a major concern for Indonesian clinicians considering the fact that the cost of both drugs is borne by the government. This systematic review, therefore, was a background to the evaluation of the effectiveness of zoledronic and ibandronic acids used during bone metastases therapy in MM. The aim of this systematic review was to describe the effectiveness of intravenous (IV) zoledronic and ibandronic acids.

MATERIALS AND METHODS

Criteria for articles in the systematic review

Research types of the article

The study involved the selection of articles based on randomized controlled trial with zoledronic acid or ibandronic acid as the intervention drugs during MM. The other drugs such as calcium and vitamin D supplements were included in the drugs given to subjects with zoledronic or ibandronic acids, as well as the comparators. Hence, the primary outcome was the incidence of SRE or PFS or OS, while the secondary was the AE. However, articles with other therapies different from bisphosphonate compounds were excluded in this research. The PRISMA performed is shown in Figure 1.

Participants

The participants were adult patients with MM, from 18-year old and above with no age limit. Articles with patients using

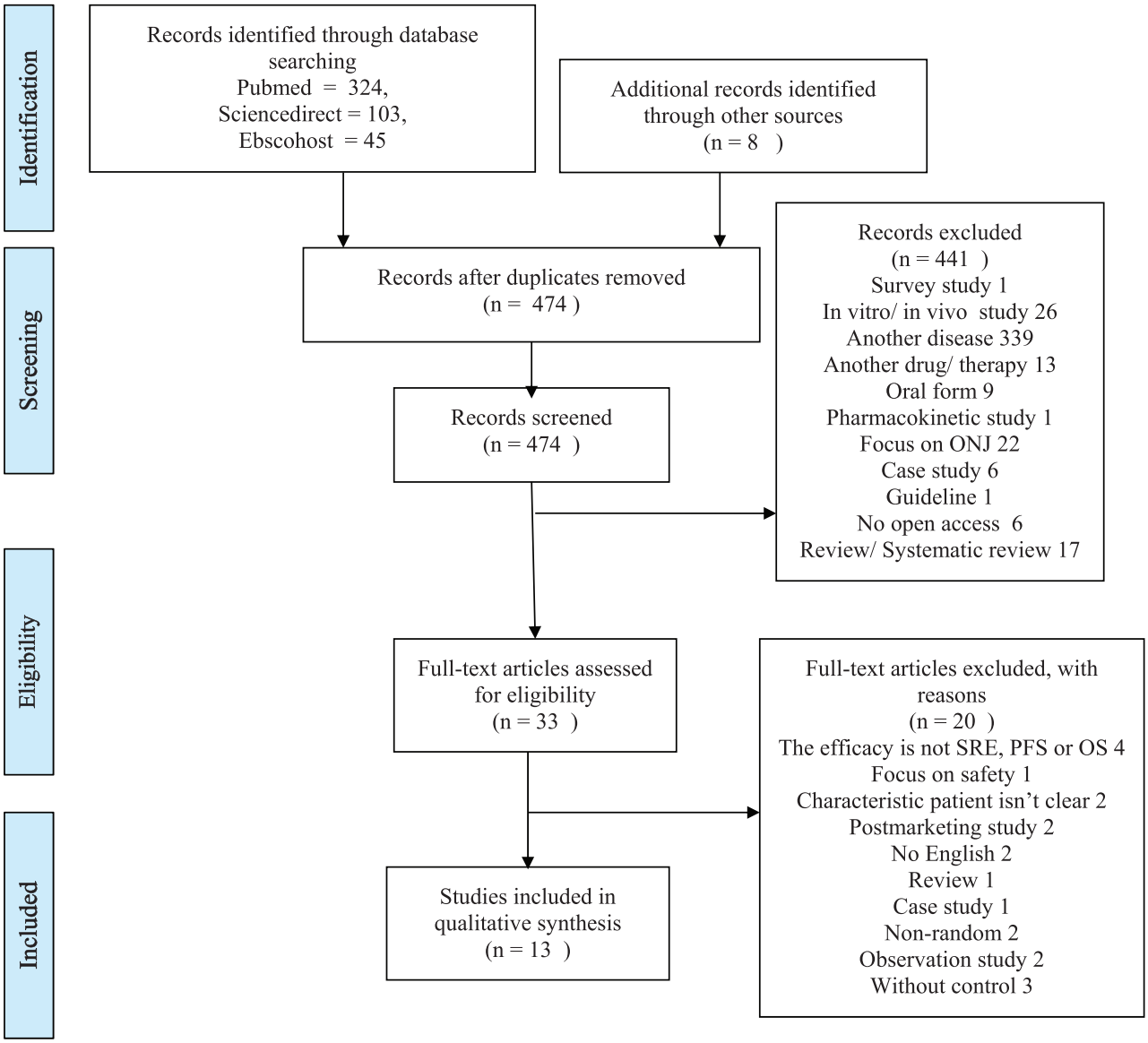

Figure 1. Selection of inclusive articles in systematic review.

different treatments as the main intervention and control in terms of using other drugs such as calcium and vitamin D supplements were excluded in the research. However, some articles did not only discuss MM patients but also were selected for review since they have data for MM patients.

Interventions and comparators

The intervention mainly was intravenous zoledronic acid or ibandronic acid while the comparator was placebo or other bisphosphonates. The dose of zoledronic acid administered was 4 mg while 2 mg or 4 mg of ibandronic acid was administered.

Outcome

The clinical outcomes were the incidence of SRE, PFS, OS, as well as some AE, such as ONJ and renal toxicity. The SRE are usually vertebral fractures or other bone fractures, and spinal cord compression, and the need for surgery or radiotherapy to the bone.

Article search method

The articles were searched in the databases of PUBMED, EBSCOhost, and ScienceDirect. The search was carried out systematically on relevant articles with restrictions to articles published within 1980 and 2018. The keyword for article search was "(ibandronate OR zoledronate) AND (bone metastasis OR metastatic bone disease OR bone pain)". These were limited to free full-text articles written in English.

Article selection and methodological quality assessment

The selection of the articles was conducted by checking the titles and abstracts of all the articles identified from the literature search results. In situations where the decision of selecting some articles was not reached based on their titles and abstracts, the full texts of such articles were considered in the process. Also, each stage of the search and screening was fully documented with the number of articles included and excluded.

The methodological quality assessment of the articles was conducted using the JADAD Score with a five-point scale, in which 1 and 2 scale are used for low-quality articles and 3 to 5 for high-quality articles.

Data extraction

The data extracted were tabulated based on the intervention, comparator, patient characteristics, and outcome. However, extraction of the intervention and comparator was performed based on the drug used, the dose and duration of intervention, while the patient characteristics were described in terms of participants' number, gender, cancer type, and MM stage. Finally, the data extraction of outcome was based on the proportion of incident of SRE, AE, PFS, and OS.

RESULTS AND DISCUSSION

Selected articles and their characteristics

In total, 13 selected articles through the RCTs met the inclusion criteria as shown in Figure 1. Comparison was conducted between zoledronic and pamidronic acid in three articles (Berenson *et al*., 2002; Rosen *et al*., 2001; 2003), three articles also compared zoledronic acid with placebo (Aviles *et al*., 2013; 2007; Garcia-Sanz *et al*., 2015), two articles compared zoledronic acid with clodronate (Morgan *et al*., 2011; 2010), two articles also compared denosumab with zoledronic acid (Henry *et al*., 2011; Raje *et al*., 2016), one research article compared ibandronic acid with placebo (Menssen *et al*., 2002), one article compared pamidronic with ibandronic acid (Terpos *et al*., 2003), and the last article compared zoledronic acid in every 12 weeks duration with every 4 weeks (Himelstein *et al*., 2017).

Five articles were with subjects not only on MM patients; two articles were on MM and breast cancer carcinoma (Berenson *et al*., 2001; Rosen *et al*., 2001); two articles were with research subjects in breast cancer and MM (Henry *et al*., 2011; Rosen *et al*., 2003), and one article was with subjects of breast and prostate cancer, as well as MM (Himelstein *et al*., 2017). Among the five articles, only Himelstein *et al*. (2017) presented data on the effectiveness of drugs in preventing SRE in MM subjects, with number as high as 139 people in each treatment group. The other four articles were added because the number of MM subjects was equivalent for each intervention group and comparator.

The treatment duration using the drug was a minimum of 10–24 months or until regression occurs. Eleven articles were with symptomatic MM as subjects and the research of Himelstein *et al*. (2017) and Garcia-Sanz *et al*. (2015) did not specifically explain the MM stage on patient characteristics. The quality of the selected articles was high, with scores between 3 and 5. Details of the explanation about the included articles are presented in Table 1.

Effectiveness of zoledronic acid and ibandronic acid

Data extraction was done to describe the effectiveness of the two drugs as shown in Table 2.

Effectiveness in reventing SRE

Four articles were zoledronic acid and placebo-controlled (Aviles *et al*., 2013; 2007; Garcia-Sanz *et al*., 2015; Menssen *et al*., 2002). The zoledronic acid has the capacity to reduce skeletal events compared to placebo by more than 50% (Aviles *et al*., 2007; Garcia-Sanz *et al*., 2015). Also, zoledronic acid was superior to placebo in preventing spinal cord compression (Garcia-Sanz *et al*., 2015). Furthermore, the incidence of radiotherapy and pathological fractures was reduced by 50% in the zoledronic acid group compared with the placebo (Aviles *et al*., 2007).

According to Berenson *et al*. (2001), Henry *et al*. (2011), Raje *et al*. (2016), and Rosen *et al*. (2001, 2003), the effectiveness of zoledronic acid was not superior to pamidronic acid or Denosumab in the prevention of SRE. At a median of 3–7 years follow-up, there was a lower SRE in the zoledronic acid group compared with the clodronic acid group. Zoledronic acid was superior to clodronic acid in preventing SRE (Morgan *et al*., 2011). According to Himelstein *et al*. (2017), 4 weeks duration of zoledronic acid was more effective than 12 weeks.

Ibandronic acid was not superior to placebo in terms of effectiveness in preventing SRE, as time to first (TTF) SRE of ibandronic acid (438 days) was not much different from placebo (462 days). According to Menssen *et al*. (2002), the pathological fracture in the ibandronic acid group (90%) during the first 6 months of follow-up was not much different from placebo (93%). Also, 20 patients (86.9%) of the pamidronic acid group and 19

Table 1. Characteristics of the included article in the systematic review.

Article	Intervention and comparator				Subject's characteristic			Jadad score
	Drug	Dose and route administration	Time duration	*N*	Gender (M/F)	Cancer type	MM Stage	
Aviles *et al*., 2007	Zoledronic Acid	4 mg IV every 4 weeks	24 months	46	26/20	MM	IIIA, IIIB	4
	Placebo			48	23/25			
Aviles *et al*., 2013	Zoledronic Acid	4 mg IV every 4 weeks	24 months	151	71/80	MM	II B, IIIA, III B	5
	Placebo			157	85/72			
Berenson *et al*., 2001	Zoledronic Acid	4 mg IV every 4 week	10 months	67	17/50	MM	III	8
	Pamidronic Acid	90 mg IV every 4 week		73	10/63	Breast Carcinoma		
Garcia-Sanz *et al*., 2015	Zoledronic Acid	4 mg IV every 4 week	12 months	51	30/21	MM	A symptomatic and no specific stage symptomatic	4
	Placebo			49	26/23			
Henry *et al*., 2011	Zoledronic Acid	4 mg IV every 4 week	24 months	890	552/338	MM	NR	8
	Denosumab	120 mg SC every 4 week		886	588/328	NSCLC Except for breast & prostate cancer		
Menssen, 2002	Ibandronic Acid	2 mg bolus IV every 4 week	12–24 months	99	53/46	MM	IIA–IIIA	8
	Placebo			99	51/48			
Morgan *et al*., 2010	Zoledronic Acid	4 mg IV every 4 week	24 months or until progression	981	589/392	MM	I, II, III	5
	Clodronic Acid	Oral 1600 mg daily		979	576/403			
Morgan *et al*., 2011	Zoledronic Acid	4 mg IV every 4 week	24 months or until progression	981	589/392	MM	I, II, III	5
	Clodronic Acid	Oral 1600 mg daily		979	576/403			
Raje *et al*., 2016	Zoledronic Acid	4 mg IV every 4 week	24 month	98	54/39	MM	I–III	7
	Denosumab	120 mg SC every 4 week		87	57/30			
Rosen *et al*., 2001	Zoledronic Acid	4 mg IV every 4 week	12 month	563	104/459	MM	III	8
	Pamidronic Acid	90 mg IV every 4 week		524	92/464	Breast Cancer		
Rosen *et al*., 2003	Zoledronic Acid	4 mg IV every 4 week	24 month	564	NR	MM	III	8
	Pamidronic Acid	90 mg IV every 4 week		558	NR	Breast Carcinoma		
Terpos *et al*., 2003	Ibandronic Acid	4 mg IV every 4 week	14 month	21	12/9	MM	IIA, IIB, IIIA, IIIB	3
	Pamidronic Acid	90 mg IV every 4 week		23	12/11			
Himelstein *et al*., 2017	Zoledronic Acid	4 mg IV every 4 week	24 month	911	414/497	MM	No specific, 199 MM patient per group.	5
	Zoledronic Acid	4 mg IV every 12 week		911	428/483	Breast Cancer Prostate Cancer		

(90.4%) of the ibandronic acid group showed no progression of bone disease during follow-up; however, pamidronic acid was superior to ibandronic acid in reducing bone resorption, interleukin -6- and β2-microglobulin pamidronate (Terpos *et al*., 2003).

Effectiveness in increasing PFS

According to Aviles *et al*. (2017), the 5-year event-free survival (EFS) of the zoledronic acid group was 80%, which is statistically different from the 52% in the placebo group ($p < 0.01$). Also, Garcia-Sanz *et al*. (2015) reported that a 3-year PFS in the zoledronic acid was 25% higher than placebo. More so, the increased PFS for 26 days in the zoledronic acid group was not significantly different from the pamidronic acid group (Rosen *et al*, 2001). According to Morgan *et al*. (2010), zoledronic acid significantly increased PFS by 12% compared to clodronic acid. In terms of median follow-up, PFS of 12 weeks duration of using zoledronic acid was more effective compared with 4 weeks (Himelstein *et al*., 2017).

Effectiveness in increasing OS

Zoledronic acid was superior to placebo in improving OS and according to Aviles *et al*. (2017) and Garcia-Sanz *et al*. (2015), there was an over 50% increment in the zoledronic acid group than the placebo. The median OS in the zoledronic acid group could not be described during follow-up, while that of the pamidronic acid group was 802 days (Rosen *et al*, 2001). According to Henry *et al*. (2011) and Raje *et al*. (2016), OS and PFS in the zoledronic acid and denosumab groups were equivalent.

The overall median survival in the ibandronic acid group (33.1 months) was not significantly different compared with the placebo (28.2 months). However, a research conducted by Menssen *et al*. (2002) stated that a small subgroup of 39 patients with WHO scored 2 to 4 at baseline and patients with VAS scores between 2 and 4 experienced significant survival benefits when treated with ibandronic acid ($p < 0.03$) and patients with radiotherapy at baseline have longer life span in the ibandronate group ($p < 0.24\%$).

Safety of zoledronic acid and ibandronic acid

The safety data of the drugs extracted are shown in Table 3. According to Garcia-Sanz *et al*. (2015), the incidence of ONJ in zoledronic acid group was greater compared with the placebo. More so, the incidence of ONJ in zoledronic acid group was not much different from the denosumab (Henry *et al*., 2011).

Table 2. The effectiveness of zoledronic acid and ibandronic acid.

Article	Intervention	*N*	Any skeletal event	Vertebral fraktur	Pathologic fraktur	Non-vertebral fracture	Spinal cord compression	Surgery to bone lesion	Radiation to bone	SRE	PFS	OS
Aviles *et al.*, 2007	Zoledronic Acid	46	10 (21)	NR	6 (13)	NR	NR	NR	8 (17)	NR	5 years EFS	5 years OS
	placebo	48	23 (47)		13 (27)				18 (37)		80% versus 84%, $p < 0.01$	80% versus 46%, $p < 0.01$
Aviles *et al.*, 2013	Zoledronic Acid	151	NR	NR	NR	NR	NR	NR	NR	NR	10 years PFS	10 years OS
	Placebo	157									66% versus 52%, $p < 0.01$	67% versus 48%, $p < 0.01$
Berenson *et al.*, 2001	Zoledronic Acid	67	22 (33)	NR	14 (21)		2 (3)	2 (3)	14 (21)	NR	NR	NR
	Pamidronic Acid	73	22 (30)		15 (21)		2 (3)	3 (4)	13 (18)			
Garcia-Sanz *et al.*, 2015	Zoledronic Acid	51	NR	NR	NR	NR	0 (0)	NR	NR	NR	3 years times free of symptom	3 years progress OS
	Placebo	49					3 (6)				32% versus 24%, $p = 0.263$	73% versus 46%, $p = 0.161$
											(the behavior of times to clinical symptoms)	
Henry *et al.*, 2011	Zoledronic Acid	890	NR	NR	NR	NR	NR	NR	NR	Median TTF	Disease progression was similar between 2 group	Similar between 2 group
	Denosumab	886								16.3 versus 20.6 month, $p = 0.06$	(HR, 1.00; 95% CI, 0.89 to 1.12; $p = 1.0$)	(HR, 0.95; 95% CI, 0.83 to 1.08; $p = 0.43$)
Menssen *et al.*, 2002	Ibandronic Acid	99	76 (77)	99 (100)	NR	89 (90)	NR	97 (98)	95 (96)	TTF 438 day	NR	Median survival
	Placebo	99	84 (85)	93 (94)		92 (93)		99 (100)	96 (97)	TTF 462 day		33.1 month versus 28.2 month
Morgan *et al.*, 2010	Zoledronic Acid	981	NR	NR	NR	NR	NR	NR	NR	NR	Median month (95% CI)	Median month (95% CI)
	Clodronic Acid	979									19.5 (9.0–38.0) versus 17.5 (8.5–34.0)	50.0 (46.0–60.5) versus 44.5 (42.0–51.5)
Morgan *et al.*, 2011	Zoledronic Acid	981	265 (27)	50 (5)	45 (5)		13 (1)	49 (5)	179 (18)	265 (27)	NR	NR
	Clodronic Acid	979	346 (35)	88 (9)	66 (7)		19 (2)	58 (6)	211 (22)	346 (35)		
Raje *et al.*, 2016	Zoledronic Acid	98	NR	NR	NR	NR	NR	NR	NR	NR	NR	No difference between the two groups. A lot of loss of follow up, will be resolved by an ongoing phase 3 trial
	Denosumab	87										
Rosen *et al.*, 2001	Zoledronic Acid	183	NR	0.27 ± 0.62	0.62 ± 1.03	0.41 ± 0.85	0.03 ± 0.22	0.05 ± 0.29	0.47 ± 3.83	MM: 86 (47)	Median time	Median OS
	Pamidronic Acid	167		0.27 ± 0.70	0.66 ± 1.17	0.45 ± 0.94	0.09 ± 0.80	0.10 ± 0.56	0.71 ± 4.12	79 (49)	136 day versus 113 day	NR versus 802 day
Rosen *et al.*, 2003	Zoledronic Acid	183	NR	NR	NR	NR	NR	NR	NR	MM: 92 (50)	Time To First SRE	NR
	Pamidronic Acid	167								92 (55)	380 day versus 286 day	
Terpos *et al.*, 2003	Ibandronic Acid	21	NR	NR	NR	NR	NR	NR	NR	2 (10)	NR	NR
	Pamidronic Acid	23								4 (17)		
Himelstein *et al.*, 2017	Zoledronic Acid 4 W	139	NR	NR	NR	NR	NR	NR	NR	84 (60)	Median time to first SRE 15.7 versus 16.8	NR
	Zoledronic Acid 12 W	139								77 (55)		

NR = not reported; a (b) = n (%); $a \pm b$ = mean ± SD; a/b (c) = n/N (%).
Data of Menssen *et al.* (2002) was proportion patient with SRE at first 3-month follow up
Data of Berenson *et al.* (2001); Henry *et al.* (2001); Morgan *et al.* (2011) were not only data of MM patient but also another cancer patient.

Table 3. Safety of zoledronic acid or ibandronic acid.

Article	Intervention	*N*	Osteonecrosis of the Jaw *n* (%)	Renal Toxicity *n* (%)
Aviles *et al*., 2007	Zoledronic Acid	46	NR	NR
	placebo	48		
Aviles *et al*., 2013	Zoledronic Acid	151	NR	NR
	Placebo	157		
Berenson *et al*., 2001	Zoledronic Acid	67	NR	NR
	Pamidronic Acid	73		
Garcia-Sanz *et al*., 2015	Zoledronic Acid	51	1 (2)	1 (2)
	Placebo	49	0 (0)	2 (4)
Henry *et al*., 2011	Zoledronic Acid	878	11 (1.3)	96 (10.9)
	Denosumab	878	10 (1.1)	73 (8.31)
Menssen *et al*., 2002	Ibandronic Acid	99	NR	Only hypocalcemia, no clinically relevant differences were found in urinary safety available
	Placebo	99		
				Acute renal failure
Morgan *et al*., 2010	Zoledronic Acid	981	21 (4)	29 (5)
	Clodronic Acid	979	2 (<1)	33 (6)
				Renal and urinary disorders
	Zoledronic Acid	981		7 (1)
	Clodronic Acid	979		8 (1)
				Acute renal failure
Morgan *et al*., 2011	Zoledronic Acid	981	35 (4)	57 (6)
	Clodronic Acid	979	3 (<1)	60 (6)
				Hypocalcemia
Raje *et al*., 2016	Zoledronic Acid	98	2 (2)	10 (11)
	Denosumab	87	4 (5)	12 (14)
Rosen *et al*., 2001	Zoledronic Acid	524	NR	NR
	Pamidronic Acid	555		
Rosen *et al*., 2003	Zoledronic Acid	524	NR	NR
	Pamidronic Acid	555		
				Hypocalcemia:
Terpos *et al*., 2003	Ibandronic Acid	23	NR	0 (0)
	Pamidronic Acid	21		2 (9)
Himelstein *et al*., 2017	Zoledronic Acid 4 W		18/911 (2)	10/852 (12)
	Zoledronic Acid 12 W		9/911 (1)	4/837 (0.5)

In addition, Raje *et al*. (2016) reported more cases of ONJ in the zoledronic acid group than the denosumab. Furthermore, there was more occurrence of ONJ in the zoledronic acid group than clodronate (Morgan *et al*., 2011). Also, 12 weeks duration of using zoledronic acid reduced ONJ more than the 4 weeks (Himelstein *et al*, 2017). According to Garcia-Sanz *et al*. (2015) and Morgan *et al*. (2011, 2010), renal toxicity in the zoledronic acid group was not different with the placebo and clodronate groups; however, the renal toxicity was higher than the denosumab group according to Henry *et al*. (2011).

Menssen *et al*. (2002) and Terpos *et al*. (2003) reported the possibility of detecting hypocalcemia after 4 weeks of ibandronic acid injection. In overall, the AE in the ibandronic acid group was the same with the placebo (Menssen *et al*., 2002) and ONJ was not reported in any of the ibandronic acid groups of the selected articles.

DISCUSSION

Zoledronic and ibandronic acids are important supportive therapies in the treatment of MM; however, there were limited evidence in the comparison of these two drugs. This study conducted a systematic review of the effectiveness of zoledronic and ibandronic acid in MM patients with intervention periods of 10–24 months. Pozzi and Raje (2011) stated that the optimal treatment duration with the use of bisphosphonates was indeed debatable but its long-term use needs to be alerted due to the occurrence of ONJ. Some guidelines suggest monthly use for 2 years based on follow-up results (laboratory data, patient

response, patient disease stability, relapse, or progression of bone disease). The Mayo Clinic guidelines suggest a monthly treatment for 2 years, terminated in patients who achieve remission or stable disease, then continue every 3 months in patients who still need more treatment. However, the International Myeloma Working Group (IMWG) stated something contrary. According to IMWG, the treatment duration of bisphosphonate needs to be adapted based on the status of the bone disease. According to Pozzi and Raje (2011), the additional use every 3 months in patients in need of more treatment or with the active bone disease was not been supported by data from the study.

Based on the systematic review, it was discovered that zoledronic acid was superior in preventing SRE compared with placebo and clodronate but not superior to other bisphosphonate compounds such as pamidronic acid and denosumab. The data for OS and PFS in the zoledronic acid group were also in line with their ability in preventing SRE.

More so, the effectiveness of ibandronic acid in preventing SRE was not superior to placebo and pamidronic acid (Menssen *et al*., 2002; Terpos *et al*., 2003). Likewise, ibandronic acid was effective in inhibiting bone resorption, interleukin-6 and β2-microglobulin, just as pamidronic acid. There was no reported data of OS and PFS with the use of ibandronic acid in the thirteen articles. This is in accordance with the statement of Geng *et al*. (2015), that ibandronic acid treats patients with metastatic breast cancer by inhibiting osteoclast activity and bone resorption, which are capable of causing osteoclast apoptosis.

However, there were more cases of AE with the use of zoledronic acid in patients compared with ibandronic acid. Based on these, it could be concluded that zoledronic acid was more effective than ibandronic acid in preventing SRE but with more occurrence of AE. Also, there were more occurrence of renal toxicity with the use of zoledronic acid. A retrospective study by Weide *et al*. (2010) with 84 MM patients who received zoledronic and ibandronic acid therapies showed that ibandronic acid produced a better renal profile than zoledronate acid. More so, there was more occurrence of the incidence ONJ and kidney damage with the use of zoledronic acid compared with ibandronic acid (Delea *et al*., 2012; Weide *et al*., 2010). The safety results of ibandronic acid in the kidneys could be used as a basis for its use for MM patients with high creatinine levels or renal disease.

ONJ was an AE associated with the use of bisphosphonates, which was first identified in 2003, several years after the introduction of pamidronic and zoledronic acids in clinical therapy (Pozzi and Raje, 2011). Some guidelines for the use of bisphosphonate compounds stated that if an ONJ case occurs, therapy must be stopped immediately until it is cured. According to Alegre *et al*. (2013), the use of zoledronic acid could be repeated as soon as the patient recovers. However, Himelstein's data (2017) showed that the incidence of AE can be reduced by extending the duration of administering zoledronic acid in each cycle. Also, there is a need for the determination of creatinine serum levels as long as zoledronic acid is used (Himelstein *et al*., 2017). More so, there is need to assess other clinical symptoms and blood tests every 3 months to examine other clinical data such as electrolytes, serum calcium levels, and albuminuria (Alegre *et al*., 2013).

The results of this research were in line with the systematic review conducted by Palmieri *et al*. (2013), which stated that zoledronic acid was more potent in the treatment of bone metastases compared with ibandronic acid. It was also considered with several MM therapy guidelines that more recommended the use of zoledronic acid than other bisphosphonates in preventing SRE. Some of the latest cancer therapy guidelines recommend zoledronic acid for the early stages of MM with the recommended dose of 4 mg IV in 15 minutes of infusion every 4 weeks. Higher doses were not recommended because of its toxicity. The treatment duration was 2 years which could be continued if the patient's needs more treatment (Alegre *et al*., 2013).

The effectiveness of zoledronic acid compared to ibandronic acid in this systematic review needs to be studied head-to-head in order to maintain the hypothesis that zoledronate is actually more effective in use in clinical practice.

CONCLUSION

In all, zoledronic acid was more effective than ibandronic acid as bone metastases therapy in MM. ONJ was more common with the use of zoledronic acid and the AE in the zoledronic acid group could be reduced by extending the treatment duration.

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CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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